16. (Amended) The method of claim 14, wherein [selecting one of more FK506 analogs comprises selecting one or more analogs of interest that bind] the non-binding FK506 analog binds FKBP-12 with a K_d of at least 30 μM.

C3

17. (Amended) The method of claim 14, wherein [selecting one or more FK506 analogs comprises selecting one or more analogs of interest that bind] the non-binding FK506 analog binds FKBP-12 with a K_d of at least 100 μM.

18. (Amended) The method of claim 14, wherein selecting [one or more FK506 analogs comprises] a FK506 analog that does not bind FKBP-12 comprises selecting one or more analogs irrespective of an activity of the one or more analogs in inhibiting FKBP-12 rotamase activity.

REMARKS

Claims 6-20 are pending. Claims 6, 7, 11-12, 14-19 are amended herein.

Claim 6 is amended to correct form. Claim 7 is amended to correctly recite the term "non-binding FK506 analog" in place of the term "agent." Antecedent basis for the term "non-binding FK506 analog" is provided in claim 6. Support for the amending language of claim 11 can be found in the specification on page 17, lines 18-19, on page 17, lines 21-29, and on page 30, lines 19-28. Claims 12 and 14-15 are amended herein to depend from claim 6, and to correct form. Claims 16-19 are amended herein to correct form. No new matter has been added. Consideration of the subject application is respectfully requested.

Applicants would like to thank Examiner Lee for the telephone conference on September 19, 2000, where she suggested that the advisory action be discussed Examiner Smith. Applicant would also like to thank Examiners Smith and Lee for conducting the telephone conference held on September 25, 2000.

Restriction Requirement

Applicants respectfully disagree with the restriction requirement imposed in the Office action dated May 15, 2000, which separates the claims into two additional groups:

The Office action states that claim 12 is a second method of identifying a non-binding FK506 analog, which has different steps and uses different reagents from the method of Group II. Applicants do not deny that claim 12 has different steps than claims 6-11; if it did not have different steps it would be reiterate the methods of claims 6-11, and could not properly be considered as a separate claim. In other words, if claim 12 consisted of identical steps to the any one of claims 6-11 it would be considered duplicative, and thus inadmissible.

However, claim 12 is directed to a method of identifying a non-binding FK506 analog, precisely what is set forth in the Office action of June 24, 1999 as being the defining feature of group II (see page 2 of the Office action dated June 24, 1999). Applicants note that claims 6-11 are all directed to a method of identifying a non-FK506 binding analog. Applicants note that the elements of the method are all included in claims 6-11 (Group II). For example, "a plurality of FK506 analogs" and "binding to FKB-12" are recited in claim 6, screening for "rotamase activity" is recited in claim 7, "selecting a FK506 analog that does not bind FKp-12" is recited in claim 6, and "assaying the FK506 analog for activity in promoting nerve cell growth" is recited in claim 6. In fact, the major difference that separates claim 12 from claims 6-11 is that claim 12 recites "selecting a FK506 analog of interest ...which has low rotamase inhibition," while claim 7 recites selecting an agent "irrespective of its ability to inhibit FKBP-12 rotamase activity." In order to clarify that claim 12 is directed to similar subject matter, claim 12 has now been amended to depend from claim 6. Reconsideration and withdrawal of the restriction requirement is respectfully requested.

A further restriction requirement is made with regard to claims 14-20. The Office action states that this restriction is made because claims 14-20 are "drawn to a method of identifying a FK506 analog that stimulates nerve cell growth [emphasis in original, see page 2]." However claims 6-12 and 14 are also directed to a method of identifying a "FK506 binding analog that stimulates nerve cell growth [emphasis added]." Again, Applicants do not deny that the steps in the method vary, otherwise the claims would be duplicative (see discussion above). Applicants can not determine the reason why the restriction requirement is made, based on the argument presented in the Office action. No separate class or subclass of original Group II is noted. Indeed, claim 14 differs from claim 6 only in that a specific K_d for binding of the FK506 analog to FKBP-12 is recited. In order to clarify that the methods are indeed related, claims 14 and 15

have now been amended to depend from claim 6. Claims 16-19 depend from claim 14. Claim 20 depends from claim 13, which was not the subject of the newly imposed restriction requirement. Reconsideration of the restriction requirement is requested.

If for any reason the restriction requirement is maintained, Applicants respectfully request specific clarification from the Examiner as to the basis of the restriction requirement for each claim in Group IV, so that they can appropriately address the Examiner's concerns.

Rejection Under 35 U.S.C. § 102

Claim 6 was rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Steiner et al., *Nature Medicine*, **3**: 421-428, 1997 (Steiner). Applicants respectfully disagree with the rejection.

The Office action alleges that the basis for the argument presented in the Amendment submitted on February 22, 2000 is that Steiner does not teach "screening" or "selecting." Steiner et al. teach that non-immunosuppressive analogs of FK506, rapamycin and cyclosporin A promote neurite outgrowth. Steiner et al. note that rapamycin binds FKBP-12 with a high affinity (see page 422, column 1, lines 7-8, and Table 1). CsA is also noted to bind FKBP-12 with a high affinity (see page 424, column 2, lines 7 to page 425, column 1, line 1, and Table 1). Steiner et al further state "There is a parallel between affinities of drugs for FKBP-12 and their potencies in stimulating neurite outgrowth..." (see page 424, column 2, lines 7-8) and "Neurotrophic potencies of the imunophilin ligands resemble their potencies in binding to and inhibiting the rotamase activity of FKP-12..." (see the abstract, page 421, lines 4-5). Thus Applicants submit that Steiner et al. teach selecting an agent that binds FKBP-12 with a high affinity, and teaches selecting an agent that specifically inhibits rotamase activity.

Claim 6 clearly recites "selecting a *FK506 analog that does not bind FKBP-12...*; [emphasis added]" thus, Steiner et al. *teach away* from the invention as claimed in claim 6. As Steiner et al. teach away from the invention as claimed in claim 6, Steiner et al. clearly cannot anticipate claim 6, or any claim that depends therefrom. Moreover, as Steiner et al. clearly *teach away from* selecting a *FK506 analog that does not bind FKBP-12*, Steiner et al. cannot suggest nor render obvious, claim 6 or any claim that depends therefrom.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejections Under 35 U.S.C. § 112, second paragraph

Claim 7 was rejected as lacking proper antecedent basis for the term "the agent." Claim 7 has been amended to recite "the FK506 analog," thereby removing the rejection.

Claim 11 was rejected as allegedly being indefinite in the use of the term "substantially." Claim 7 has been amended to recite that the FK506 analog does not "significantly" inhibit rotamase activity. Assays for rotamase activity are well known in the art and are described in the specification on page 17, lines 21-29. Using the description in the specification, and the indicated references (Harding et al., *Nature* **341**: 758-760, 1989; Siekierka et al., *Nature* **341**: 755-757, 1989, see the specification on page 17, line 22) one of skill in the art would readily be able to ascertain a significant inhibition of rotamase activity. Thus, Applicants submit that the amendment of the claim 11 renders it definite.

Reconsideration and withdrawal of the rejection are respectfully requested.

New Rejections Under 35 U.S.C. § 102

Claims 6-11 and 13 were rejected as allegedly being anticipated by Steiner et al. (U.S. 5,801,197, herein after the '197 patent). Applicants respectfully disagree with the rejection as applied to claims 6-11 and 13, and as may be applied to claims 12 and 14-20.

The '197 patent discloses FKBP rotamase inhibitors that *have* an affinity for FKBP-12 (see column 1, first paragraph, line 2, column 2, lines 60-61, and column 4, lines 13-15). Thus, the '197 patent *teaches away* from selection of an FK506 analog that *does not bind* FKBP-12, as specified in claims 6-11 and 13.

The Office action points to column 7 as teaching methods of identifying a non-binding FK506 analog. However, column 7 notes the close correlation between the potencies of drugs and their bindings to immunophilins (FKBP-12, e.g. see lines 7-8), and describes how rotamase inhibition is involved in the effects (e.g. see lines 16-18). Thus, the '197 patent *teaches away* from the use of FK506 analogs that do not bind FKBP-12, and thus does not anticipate, nor render obvious, claims 6-11 (or claims 12 and 14-20).

A general compound structure is shown in column 7, which is noted to be a general formula for FK506 inhibitors. Applicants do not deny that compounds of this formula can be included in claim 13, however, claim 13 depends from claim 6, and thus those compounds are

clearly limited to compounds that *do not bind FKBP-12.* However the '197 patent discloses compounds of this formula are illustrative of agents that bind FKBP-12 with a high affinity (see column 7, lines 3-4). Applicants submit that a compound of the general formula shown in column 7 can either 1) bind FKBP-12 with a high affinity or 2) not bind FKBP-12, but clearly cannot do both. Thus, the set of compounds disclosed in the '197 patent is clearly distinct from the set of compounds as claimed in the subject application, even though both sets of compounds are encompassed by the formula shown. Thus, the disclosure of the '197 patent, which includes compounds that bind FKBP-12 do not anticipate, nor render obvious, the compounds of claims 6-11 or 13, which do not bind FKBP-12.

Reconsideration and withdrawal of the rejection is respectfully requested.

Conclusion

Applicants believe the claims are now in condition for allowance. If any matters remain to be resolved before a Notice of Allowance is issued, the Examiner is invited to telephone the undersigned patent attorney at the telephone number listed below.

Respectfully submitted,

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